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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 23 1999

Lorna C. Totman, Ph.D., DABT
Director of Scientific Affairs
Nonprescription Drug Manufacturers Association
1150 Connecticut Avenue, N.W.
Washington, D.C. 20036

Re: Docket No. 78N-036L
Comments No. PR5 and C195

Dear Dr. Totman:

Reference is made to the information submitted on behalf of the Nonprescription Drug Manufacturers Association (NDMA) Bisacodyl Task Group, dated September 16 and 17, 1998. The submissions are identified as Comments No. PR5 and C195, respectively, filed under Docket No. 78N-036L in the Dockets Management Branch.

You submitted the following information to support the safety of bisacodyl as a Category I over-the-counter (OTC) laxative drug ingredient: (1) Mutagenicity study reports for bisacodyl conducted in Chinese hamster ovary cells (CHO) mammalian cell hypoxanthine guanine phosphoribosyl transferase (HGPRT) forward gene mutation and Syrian hamster embryo (SHE) cell transformation assays, (2) single dose pharmacokinetic studies with different formulations of bisacodyl in healthy human volunteers, (3) single day pharmacokinetic studies in CD-1 and C57BL/6 mice (i.e., wild strain of C57BL/6TacfBR-[KO]p53 mice), (4) a 4-week oral dose range finding study in C57BL/6 mice, (5) a 13-week oral dose range finding study in CD-1 mice, and (6) a draft protocol for a 26-week oral carcinogenicity study using heterozygous C57BL/6TacfBR-[KO]p53 (TSG-p53™) mice.

We have reviewed the data and study protocols, and have the following comments.

The mutagenic potential of bisacodyl was assessed in the CHO (HGPRT) forward gene mutation assay. A preliminary solubility test determined that bisacodyl was insoluble in aqueous media at concentrations equal to or greater than 153 micrograms (ug)/milliliter (mL). For the mutation assay, bisacodyl was tested at concentrations of 5, 10, 25, 50, and 100 ug/mL in the presence and absence of metabolic activation. There was no significant increase in the mutant frequency at any bisacodyl concentration either in the presence or absence of metabolic activation. Expected responses were obtained with positive controls, 3-methylcholanthrene and ethyl methansulfonate, in the presence and absence of metabolic activation, respectively. Bisacodyl was negative in the CHO HGPRT forward gene mutation assay at concentrations ranging from 5 to 100 ug/mL. There was no evidence of cytotoxicity at any concentration in the presence or absence of metabolic activation.

Bisacodyl was found to be negative in the SHE in vitro cell transformation assay. Morphological transformation was unaffected by exposure to bisacodyl concentrations of 45, 60, 75,

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90, and 100 ug/mL for the 24 hours. The highest concentration, 100 ug/mL, produced precipitation as well as a decrease in the relative plating efficiency to 61 percent. Morphological transformation was unaffected by exposure to bisacodyl concentrations of 30, 35, 40, 45, and 50 ug/mL for 8 days. In the first 8 day exposure assay, relative plating efficiency at 50 ug/mL was 64 percent. In the second 8 day exposure assay, plating efficiency ranged from 67 to 76 percent at concentrations from 30 to 55 ug/mL. Morphological transformation was unaffected by exposure to bisacodyl concentrations of 50 and 55 ug/mL.

In the single dose human study, plasma levels of glucuronidated bisacodyl were correlated with onset of laxative effect. Twelve healthy human volunteers (6 men and 6 women) received 10 milligram (mg) of bisacodyl either as an oral 0.05 molar (M) aqueous hydrochloric acid solution (pH 1.7), two oral 5 mg commercially coated tablets, or one commercial suppository. The three different formulations were administered on different days with a 3 or 4 day washout period between each formulation. Following administration of bisacodyl in aqueous hydrochloric acid solution, systemic levels of the bis-(p-hydroxyphenyl) pyridyl-2-methane (BHPM) monoglucuronide were approximately 10 to 20 times higher than tablet or suppository. Urinary excretion of BHPM monoglucuronide was higher following administration of bisacodyl in aqueous hydrochloric acid solution as compared with tablet or suppository. Laxative action was not found to correlate to systemic levels of BHPM monoglucuronide.

In the one-day rodent study, the pharmacokinetic profile of bisacodyl was evaluated in male and female CD-1 and C57BL/6 mice following one day of oral administration. Animals received bisacodyl by oral gavage at doses of 40, 4000, or 8000 mg/kilogram (kg)/day. Animals in the control and 8000 mg/kg/day group received the vehicle or test article, respectively, in two divided doses administered 4 hours apart. The dose volume was 20 mL/kg. For both CD-1 and C57BL/6 mice, plasma Cmax and AUC values for the glucuronide conjugate of bisacodyl generally increased with increasing dose; however, values were not proportional to dose. Tmax values increased with increasing dosage. There were no significant differences in plasma Cmax and AUC values for conjugated bisacodyl between male and female mice. Levels of the free diphenol of bisacodyl were only detected with a dose of 8000 mg/kg/day and constituted a small fraction (generally <5 percent) of the total glucuronidated bisacodyl concentrations. A terminal elimination phase was not apparent for all treatment groups at 28 hours after dosing.

In the 4-week dose range finding study, C57BL/6 mice received bisacodyl by oral gavage at doses of 0, 40, 4000, and 8000 mg/kg/day. Animals in the control and 8000 mg/kg/day groups received the vehicle or test article, respectively, in two divided doses administered 4 hours apart. Soft and light colored stools were observed for male and female mice at doses of 4000 and 8000 mg/kg/day during week 1. Soft stools appeared to be a transient effect; although light colored stools were observed throughout the treatment period. The dose of 8000 mg/kg/day appears to represent the maximum feasible dose. A 200 mg/mL suspension of bisacodyl in the vehicle was used for the 4000 and 8000 mg/kg/day treatment groups. The dosing volume was 20 mL/kg, which exceeds the recommended dose volume by at least two times (Principles and Methods of Toxicology 3rd edition, Raven Press, 1994, Page 703). The 4-week dose range finding study was

deficient due to the lack of hematology, blood biochemistry, urinalysis, and physical examinations. A target organ of toxicity was not identified. We also have some concern that the mice might be unusually resistant to the toxic potential of bisacodyl. The maximum tolerated dose for both CD-1 and C57BL/6 mice appears to exceed 8000 mg/kg/day. As noted in the "Journal of Toxicology and Environmental Health 39:59-78, 1993," when Fischer-344 rats received bisacodyl in their diet at doses of 24, 80, and 240 mg/kg/day for periods of 8, 16, 24 and 32 weeks, the male rats receiving bisacodyl at 240 mg/kg/day for periods of 16 to 32 weeks, developed urinary bladder calculi. Histological examination of the urinary bladders showed epithelial proliferative lesions that included hyperplasia, papillary hyperplasia, nodular hyperplasia, and papillomatosis.

In the draft report of the 13-week oral dose range finding toxicity study, CD-1 mice received bisacodyl by oral gavage. The dose of 8000 mg/kg/day administered for 9 weeks appeared to be well tolerated and appeared to be the maximum feasible dose. The incidence of soft and light colored stools and number of animals affected increased in a dose-related manner. There were no treatment-related alterations of the frequency of micronuclei in polychromatic (PCE) or normochromatic erythrocytes (NCE) as well as the PCE/NCE ratio for both peripheral blood and bone marrow, and no target organ(s) of toxicity were identified. On day 1 following administration of doses of 5, 10, and 40 mg/kg/day, plasma levels of the glucuronide conjugate of bisacodyl were approximately proportional to dose. On days 42 and 85 following administration of doses of 40, 4000, and 8000 mg/kg/day, plasma levels of the glucuronide conjugate increased with dose; although levels were not proportional to dose. There were no significant differences in plasma levels of conjugated bisacodyl between male and female mice. Levels of the free diphenol of bisacodyl were only observed at doses of 4000 and 8000 mg/kg/day and constituted less than 1 percent of the total conjugated bisacodyl concentrations. We conclude that this study was deficient due to the lack of hematology, blood biochemistry, urinalysis, and physical examinations.

The draft protocol for the evaluation of the carcinogenic potential of bisacodyl proposed to study heterozygous TSG-p53™ mice for 26 weeks. TSG-p53™ mice will receive bisacodyl by oral gavage at doses of 0, 800, 4000, and 8000 mg/kg/day. Animals in the control and 8000 mg/kg/day groups will receive vehicle or test article, respectively, in two divided doses administered 4 hours apart. The dose volume will be 20 mL/kg. Bisacodyl doses were selected using the 4-week dose range finding study in C57BL/6 mice described above. Selection of 8000 mg/kg/day as the high dose in the TSG-p53™ mouse carcinogenicity study appears to be justified as it represents the maximum feasible dose. A 200 mg/mL suspension of bisacodyl in 1 percent carboxymethylcellulose/0.2 percent Tween 80 will be used for the 4000 and 8000 mg/kg/day treatment groups.

We have the following recommendations regarding the proposed 26-week study. The draft protocol for assessing the carcinogenic potential of bisacodyl using heterozygous TSG-p53™ mice appears to be acceptable with some modification. Selection of 8000 mg/kg/day as the high dose in the TSG-p53™ mouse carcinogenicity study appears to be justified as it represents the

maximum feasible dose. However, we are concerned that the use of an unusually high dose volume of 20 mL/kg might lead to excessive mortality over a 26-week period. We note that the dosing volume of 20 mL/kg exceeds the recommended dose volume by at least two times. The dose volume for the positive control group should be identical to that used for bisacodyl treatment groups because the doses of 800, 4000, and 8000 mg/kg/day in the C57BL/6 mice in the 4-week study exceeded the human dose of 0.2 mg/kg by 400; 20,000; and 40,000 times, respectively. Also, sufficient toxicokinetic data was not submitted in the 4-week dose range finding study to use a limit dose of 1500 mg/kg/day. We recommend that the doses be 500, 2000, and 8000 mg/kg/day, respectively. Further, the dose volume for the vehicle and positive control groups as well as bisacodyl groups at 500 and 2000 mg/kg/day should be no more than 10 mL/kg.

In addition, all tissues listed in the protocol should be collected and preserved for the vehicle and positive control groups as well as bisacodyl groups at 500, 2000, and 8000 mg/kg/day. Histopathological examinations of tissues from any of the bisacodyl groups beyond those listed in the protocol under any of the following circumstances should be conducted: (a) Any macroscopic findings in the 500 and 2000 mg/kg/day groups; (b) an increase in the incidence of tumors (rare or common) observed in the 8000 mg/kg/day group for a particular tissue, even if not statistically significant; (c) any increases in tumors analyzed across tissues sites as well as by tissue site will require all relevant tissues from that dose level and the next lower dose level to be examined; and (d) an excessive decrease in body weight or survival in the examined dose group.

In conclusion, we have determined that the data indicate that bisacodyl has no mutagenic potential either in the CHO (HGPRT) forward gene mutation or in the SHE in vitro cell transformation assays. The draft protocol for the 26-week study in C57BL/6 mice should be revised as discussed above. If treatment-related tumorigenic findings occur in TSG-p53™ mice, a 13-week dose range finding and 2-year carcinogenicity studies in rats will be needed. The Fischer 344 rat appears to be a more suitable model for assessing the potential toxicity of bisacodyl than either the C57BL/6 or CD-1 mice. Therefore, if a 13-week dose range finding study and a 2-year carcinogenicity study are needed, we recommend that Fischer 344 rats be used. However, if no treatment-related tumorigenic findings occur in TSG-p53™ mice, a 2-year carcinogenicity study in rats may not be necessary due to the overall negative findings with bisacodyl to date, and the negative rat bone marrow micronucleus assay (see LET175, Docket No. 78N-036L).

Any comment you wish to make on the above information should be submitted in three copies, identified with the docket number shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

We hope this information will be helpful.

Sincerely yours,

Debra L. Bowen
Acting Director
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc: Dr. Soller, NDMA
David R. Brill, Ph.D. (Boehringer Ingelheim)

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: MAR 30 1999 7179 '99 MAR 31 P2:26

OTC

FROM: Director
Division of OTC Drug Evaluation, HFD-560

SUBJECT: Material for Docket No. 78N-036L

TO: Dockets Management Branch, HFA-305

[X] The attached material should be placed on public display under the above referenced Docket No.

[X] This material should be cross-referenced to Comment No. PR5 & C195.

Debra L. Bowen

Debra L. Bowen, M.D.

Attachment